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Development and Mechanistic Study of Quinoline-Directed Acyl C−O Bond Activation and Alkene Oxyacylation Reactions

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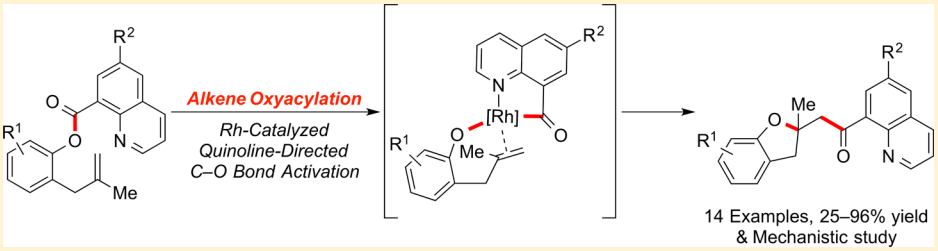
Supporting Information



ABSTRACT: The intramolecular addition of both an alkoxy and acyl substituent across an alkene, oxyacylation of alkenes, using rhodium catalyzed C−O bond activation of an 8-quinolinyl ester is described. Our unsuccessful attempts at intramolecular carboacylation of ketones via C−C bond activation ultimately informed our choice to pursue and develop the intramolecular oxyacylation of alkenes via quinoline-directed C−O bond activation. We provide a full account of our catalyst discovery, substrate scope, and mechanistic experiments for quinoline-directed alkene oxyacylation.

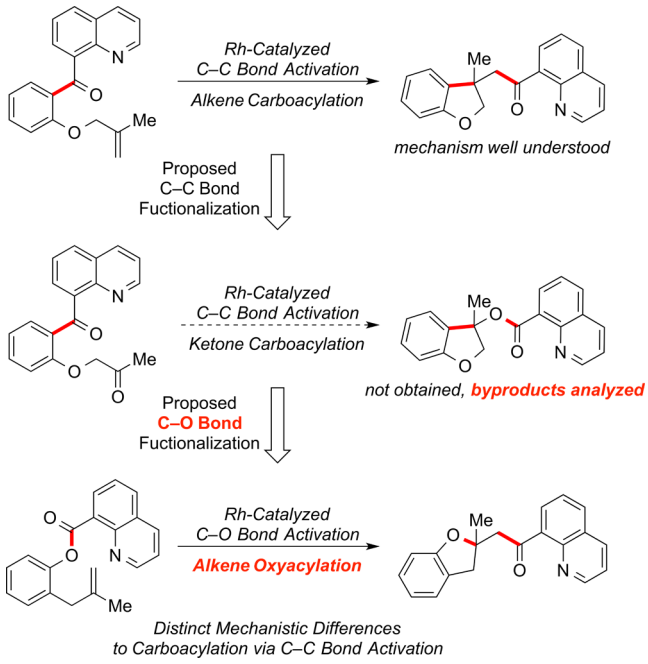
INTRODUCTION

The activation and functionalization of C−C and C−O bonds adjacent to carbonyl groups is a powerful new strategy for catalysis in organic synthesis. The field of catalytic C−C bond activation is rapidly growing and has been the subject of several recent reviews and books.[1] With the notable exception of nitriles,[2] much of the recent work in this area has focused on strained ring systems.[3] Our early efforts focused on metal catalyzed activation of unstrained C−C bonds to trigger the carboacylation of alkenes.[4] Alkene carboacylation is an atom-economical and complexity-building reaction when it is initiated by C−C bond activation of a ketone. We employed covalently attached directing groups to facilitate bond activation of unstrained ketones for alkene carboacylation. Our initial work used the quinoline ring system as the directing group. Our work with quinoline ketones indirectly led us to the analogous chemistry of esters that involves C−O bond activation.

In this article, we describe how byproduct analysis from failed experiments aimed at ketone carboacylation via C−C bond activation inspired our work in acyl C−O bond activation with esters (Scheme 1). Acyl C−O bond activation of esters enables the addition of the acyl group and the alkoxy group of an ester across an alkene, a process we name alkene oxyacylation. We present our mechanistic study and further optimization of the alkene oxyacylation reaction. Our results show that the mechanism of intramolecular alkene oxyacylation is similar, but distinct, from alkene carboacylation.

The 8-subsituted-quinoline ring system has a long history in the activation of carbon sigma bonds. Suggs pioneered the use of quinoline directing groups in the C−H activation of 8-

Scheme 1. Discovery and Development of C−C and C−O Bond Activation with 8-Acyl Quinolines



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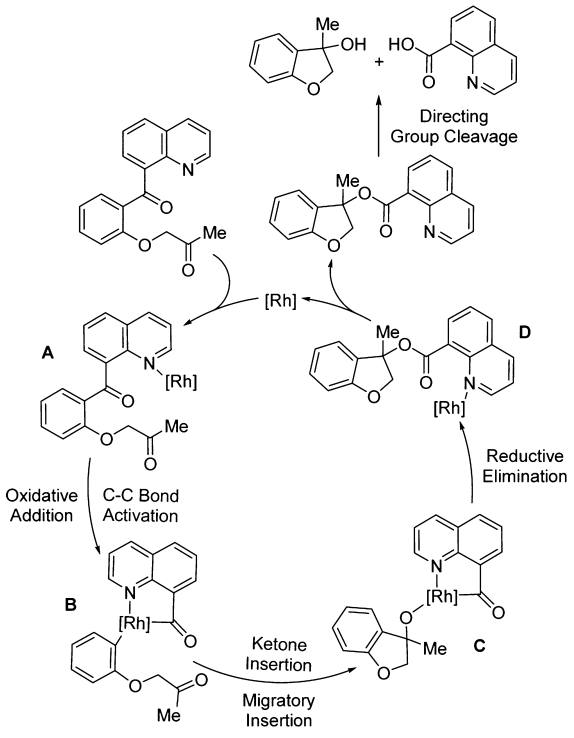
quinolinecarboxyaldehyde. The quinoline group forms a stable, 5-membered ring through cyclometalation, which prevents decarbonylation and provides a chelate effect to promote oxidative addition.[5] Although C−C bond activation is more challenging than C−H activation, Suggs and Jun were able to use the quinoline directing group to activate α-ketone C−C bonds. They selectively activated this C−C bond since the ketone functionality weakens the adjacent bond and cyclometalation preferentially forms 5 membered rings.[6] We have previously shown that quinoline-based directing groups can facilitate intramolecular carboacylation of alkenes.[4] Coordination of the quinoline directing group brings the catalyst close to the desired C−C bond and stabilizes reactive intermediates in the catalytic cycle, promoting alkene carboacylation. The stability of the resulting metallacycle also slows decarbonylation, which may occur after bond activation adjacent to a carbonyl.[7]

Utilizing the 8-acyl quinoline directing group, we obtained carboacylation products in up to 96% yield. Recognizing the challenge of removing the quinoline directing group,[8] we proposed intramolecular carboacylation of a ketone using the same directing group (Scheme 1, middle); successful C−C bond activation and ketone carboacylation would generate an ester, allowing for directing group cleavage.

Johnson has studied the mechanism of alkene carboacylation.[9,10] He found that resting state resulted from coordination of the rhodium metal to the nitrogen of the quinoline directing group. We propose a similar step for ketone carboacylation to generate intermediate **A** (Scheme 2). Next, we proposed that rhodium(I) would undergo oxidative addition into the C−C bond adjacent to the quinolinyl ketone to form metallacycle **B**. In alkene carboacylation, Johnson showed that the C−C activation step was rate-limiting. For our proposed ketone carboacylation, intramolecular migratory insertion across the ketone would generate intermediate **C**. Late-metal alkyl or aryl groups rarely react with aldehydes or ketones via migratory insertion;[11] therefore, our proposed transformation hinges upon this challenging migratory insertion event. Reductive elimination of intermediate **C** would form the C−O bond in ester **D**. Dissociation of the metal would then yield the product and regenerate the active catalyst.

Scheme 2. Proposed Catalytic Cycle for Ketone Carboacylation



RESULTS AND DISCUSSION

Substrate Synthesis for Ketone Carboacylation. For the initial investigation of intramolecular ketone carboacylation, compounds **1a** and **1b** were synthesized (Scheme 3).[12] 8-Bromoquinoline underwent lithium halogen exchange and the resulting organolithium was added to PMB protected salicylaldehyde. Oxidation of the resulting secondary alcohol by IBX was followed by PMB deprotection using TFA to give phenol **3** (64% yield over 3 steps).[4] Initial attempts to convert phenol **3** to ketone **1a** via S_N2 displacement indicated that once ketone **1a** formed, it underwent an intramolecular aldol reaction to form product **2a**. We obtained a 50% yield of **1a** along with a 31% yield of **2a** by using a substoichiometric amount of base (NaH 0.95 equiv) and carefully monitoring the reaction by TLC. We could avoid the aldol reaction for methyl ketone product **1b** at low conversion of phenol **3**. We obtained a 35% yield of **1b** and recovered 63% of **3**, while only detecting trace amounts of the aldol product **2b**.

Attempted Ketone Carboacylation and Byproduct Analysis. We began our attempts at ketone carboacylation with Wilkinson's catalyst based on its success in the alkene carboacylation transformation.[4] We heated ketone **1b** with Wilkinson's catalyst. The ^{1}H NMR spectrum of the crude reaction mixture showed the formation of a new product displaying geminal diastereotopic protons (Scheme 4a). We expected these diastereotopic signals for the carboacylation product; however, we also observed many unexpected aromatic signals. Seeking to identify this new product, ketone **1b** and Wilkinson's catalyst (1 equiv) were allowed to react for 4 h in CH_2Cl_2 under ambient conditions. The same new compound formed and we isolated it in 93% yield after column chromatography.

The ^{1}H NMR spectrum of this new product showed diastereotopic hydrogen signals at 4.4 and 4.0 ppm that were consistent with the proposed 2,3-dihydrobenzofuran ring structure (Scheme 4a). Additional aromatic signals remained in the purified product. We turned to ^{31}P NMR to determine if these signals corresponded to triphenylphosphine. ^{31}P NMR showed two inequivalent phosphorus signals, 13.34 (dd, J = 128.1, J = 32.1 Hz), 10.94 (dd, J = 114.8, J = 32.1 Hz).[13] We assigned the smaller coupling constant to geminal ^{31}P coupling and the larger coupling to a rhodium center. The small coupling constant suggested that two triphenylphosphine ligands were *cis* to one another on a rhodium center.[14] We also observed only one carbonyl signal by IR. Characterization of quinoline containing rhodium(III) complexes by Suggs and Jun led us to tentatively assign the complex as **4** (Scheme 4c).[15] Structure **4** was appealing since it could result from C−C bond activation and migratory insertion. To test our hypothesis, we scaled up the synthesis of this complex to obtain ^{13}C NMR data. We confirmed that only one carbonyl carbon was present, however, the anticipated Rh splitting of the carbonyl carbon was not observed. Instead, we observed a peak at 106.2 ppm, a doublet with a coupling constant of 3.8 Hz (Scheme 4b).

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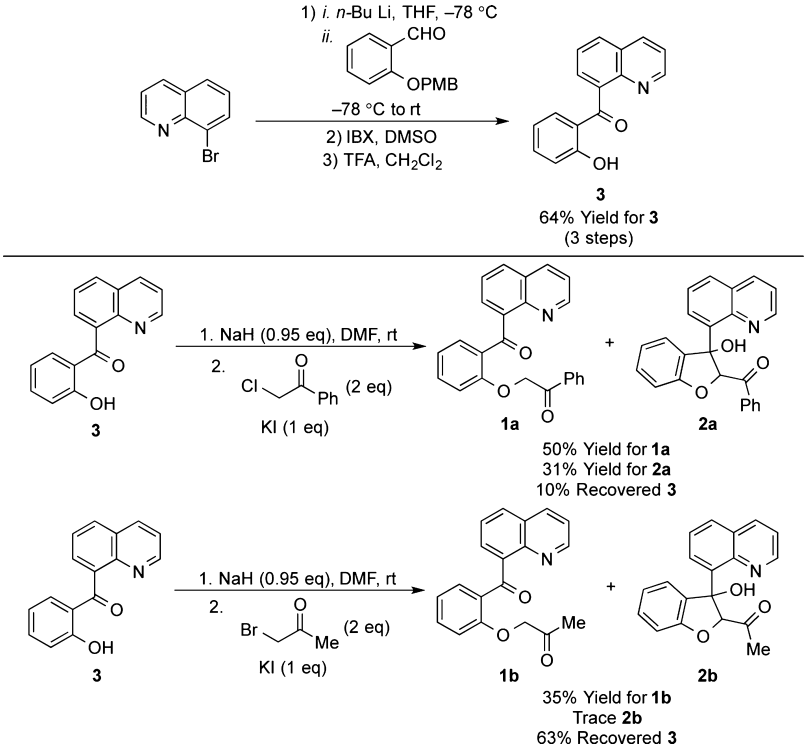
Scheme 3. Ketone Carboacylation Substrate Synthesis



Analysis of an HMBC spectrum revealed that the methyl hydrogens were adjacent to the carbonyl carbon, a result not consistent with structure **4**. Additionally, we observed the carbon at 106.2 ppm display long-range coupling to an aromatic hydrogen on the quinoline group and additional aromatic group (Scheme 4c and d). While these data forced us to rule out structure **4**, the diastereotopic signals require chirality in the structure. Flummoxed, we sought to solve the structure by single crystal X-ray diffraction.

After screening a variety of solvent systems, we obtained single crystals from a dichloromethane:pentane mixture that allowed us to assign the structure of the rhodium complex. The crystal structure revealed that complex **5** incorporated O_2 (Scheme 4e and f). Incorporation of O_2 is known with rhodium species, specifically with Wilkinson's catalyst.[16,17] We know of only one other example in which molecular oxygen has bonded to both a rhodium and a carbon atom.[17] Heating the complex resulted in the release of **1b**, as determined by in situ NMR spectroscopy. Prolonged heating led to slow formation of triphenylphosphine oxide.

Concurrent with our investigation with Wilkinson's catalyst, we examined $[Rh(C_2H_4)_2Cl]_2$ for reactivity toward ketone carboacylation. Upon treatment of **1a** or **1b** with $[Rh(C_2H_4)_2Cl]_2$ (5–20 mol%), we observed new compounds by ^1H NMR in the crude reaction mixtures. The yields of these compounds were dependent on the rhodium loading. When rhodium loading was increased to 1 equiv (50 mol% of $[Rh(C_2H_4)_2Cl]_2$), two compounds were isolated from the reaction with **1a**, and three compounds were isolated from the reaction with **1b**. To our surprise, none of these compounds contained the quinoline directing group. We identified the new compounds as alkene **6**, *trans*-alkene **7**, and alcohol **8** (Scheme 5). Treatment of **1a** or **1b** under the reaction conditions without $[Rh(C_2H_4)_2Cl]_2$ indicated that **1a** and **1b** undergo intramolecular aldol cyclizations to a small extent (<10%) at high temperature; aldol byproducts **2a** or **2b** were observed in most reactions.

We rationalized the formation of **6**, **7**, and **8** through the mechanistic pathways outlined in Scheme 5. Upon heating, $[Rh(C_2H_4)_2Cl]_2$ undergoes oxidative addition with **1a** or **1b** to form an alkyl rhodium complex **B** with the loss of 1 equiv of ethylene. The Rh(III)–C bond in **B** can then undergo migratory insertion across the tethered ketone C=O π or the C=C π bond of an ethylene ligand, forming complex **C** or compound **6**, respectively. In the reaction with **1b**, intermediate **B** also undergoes two ethylene insertion reactions, followed by alkene isomerization, to form **7b**. Rhodium complex **C** could decompose to form alcohol **8**. An alternative explanation for the formation of alcohol **8** is the hydrolysis of ester **D** (our desired product); however, we found no evidence for this ester. On the contrary, others have reported the formation of alcohols from rhodium(III) alkoxides analogous to **C**.[11] Although Suggs and Jun reported chemistry similar to the styrene formation, we observed,[18] we are unaware of reports on forming an alcohol similar to **8** via C–C σ bond activation and migratory insertion across C=O π bond.

Since we were able to isolate alcohols **8a** and **8b**, but not the desired ester product, we questioned if our proposed reductive elimination was unfavorable. The formation of **8a** and **8b** indicated intermediate **C** had formed. We then speculated that oxidative addition of Rh(I) to an 8-carboxy quinoline ester would be favorable, since the resulting complex would be similar to intermediate **C**.[19] To test this hypothesis, we designed substrate **16** (Scheme 6) to attempt oxidative addition into an ester followed by migratory insertion across a tethered alkene. Reductive elimination would yield a ketone in a catalytic manner.

Substrate Synthesis for Acyl C–O Bond Activation. Scheme 6 shows the routes for synthesizing alkene oxyacylation substrates. We synthesized phenols **10a–j** and **15** by

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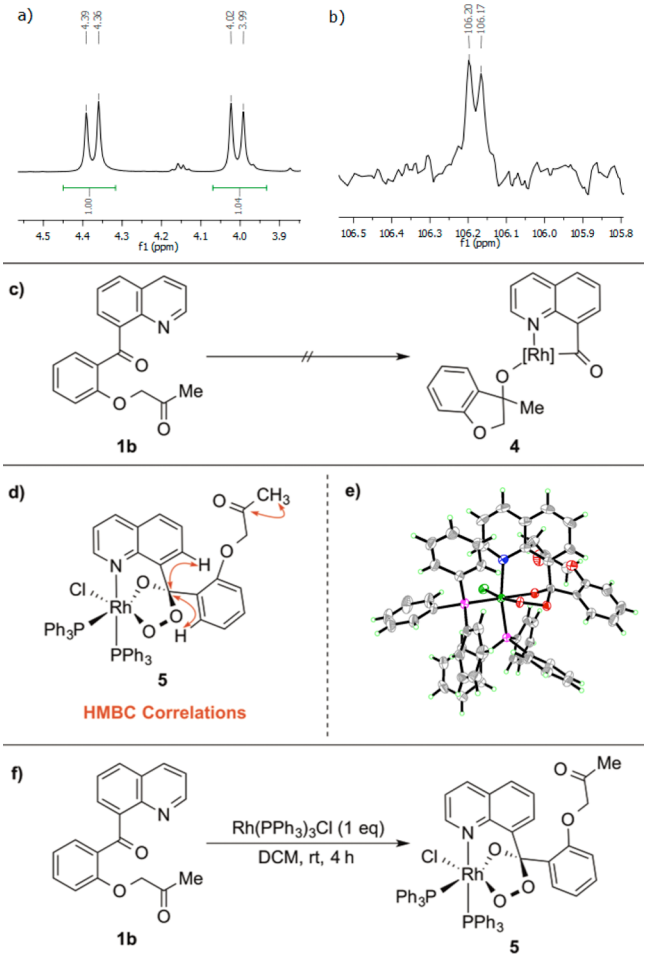
Scheme 4. Structural Determination of Rhodium Complex[a]



[a](a) ^{1}H NMR of nonequivalent alkane hydrogens. (b) ^{13}C NMR of quaternary carbon. (c) Initially proposed reaction of **1b** with Wilkinson's catalyst. (d) Diagnostic HMBC correlations. (e) ORTEP drawing of complex **5**. (f) Reaction of **1b** with Wilkinson's catalyst.

Williamson ether synthesis to yield aryl ethers **9a–j** and **15**. Subsequent Claisen rearrangements of **9a–j** yielded ortho allyl phenols **10a–j**. Phenol **14** was synthesized in 2 steps from 2-methoxybenzyl chloride according to a known procedure.[20]

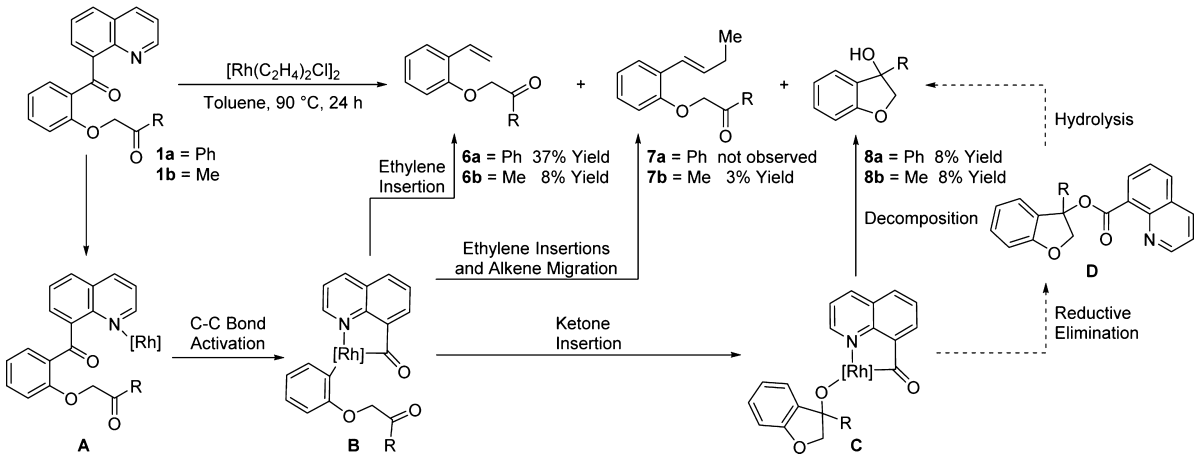
The Skraup reaction could be used to prepare 8-bromoquinoline **11a** or 8-bromo-6-methylquinoline **11b**. These 8-bromoquinolines were converted to the 8-quinolinecarboxylic acids **12a–b** via quenching the corresponding organolithium reagents with CO_2.[21] A DCC esterification of the ortho allyl phenols with the 8-quinolinecarboxylic acids yielded the target substrates for alkene oxyacylation.

Discovery of Intramolecular Alkene Oxyacylation Reaction. We initially attempted alkene oxyacylation of **16a** with a variety of rhodium alkene complexes in toluene at 130 °C with no added ligands (Table 1, Entries 1–3). In the reaction with Rh(cod)$_2$OTf, we observed oxyacylation product **17a** and phenol **10a**, a byproduct resulting from formal hydrolysis of ester **16a** (Entry 3). Molecular sieves did not improve the **17a**:**10a** ratio (not shown). The rhodium complex's poor solubility in toluene led us to examine alternative solvents. 1,2-Dichloroethane (DCE) gave homogeneous reaction mixtures and product **17a** was obtained in 40% yield with Rh(cod)$_2$BF$_4$ (Entry 4). The reaction with Rh(cod)$_2$OTf in DCE led to a complex mixture (Entry 5).

We selected Rh(cod)$_2$BF$_4$ in DCE for further optimization with added phosphine ligands. During the initial attempts, we noted a concentration effect; higher concentrations of **16a** or catalyst led to more byproduct **10a** (not shown in Table 1). Thus, in subsequent reactions, we used more dilute substrate concentrations (0.05 M) and lower catalyst loadings (10 mol %). We tested three bidentate phosphine ligands (Entries 6–8). The ligand with the lowest bite angle (dppe, 82.55°) resulted in no reaction. The intermediate bite angle ligand (dppp, 91.56°) was more effective than the ligand with the largest bite angle (dppb, 97.07°).[22] The reaction using Rh(cod)$_2$BF$_4$ and dppp in DCE at 130 °C gave the oxyacylation product in 82% yield (isolated) with less than 10% yield of byproduct **10a** (Table 1, Entry 8).

Both the yield of **17a** and ratio of **17a**:**10a** were dependent on reaction temperature. Treating **16a** with the Rh(cod)$_2$BF$_4$/dppp catalyst at 90 °C, we observed the oxyacylation product **17a**, but the reaction did not reach completion in 24 h and the ratio **17a**:**10a** was 1:1 (Entry 9). Temperatures below 90 °C only gave the byproduct **10a**. Increasing the temperature provided better conversion and lower amounts of byproduct (Entries 10 and 11). Reaction at 150 °C in toluene:DCE (8:2) proved optimal, providing the product in 85% isolated yield with trace amount of **10a** (Entry 11). A solvent mixture of

Scheme 5. Proposed Mechanistic Pathway to Observed Products



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Scheme 6. Substrate Synthesis For Alkene Oxyacylation

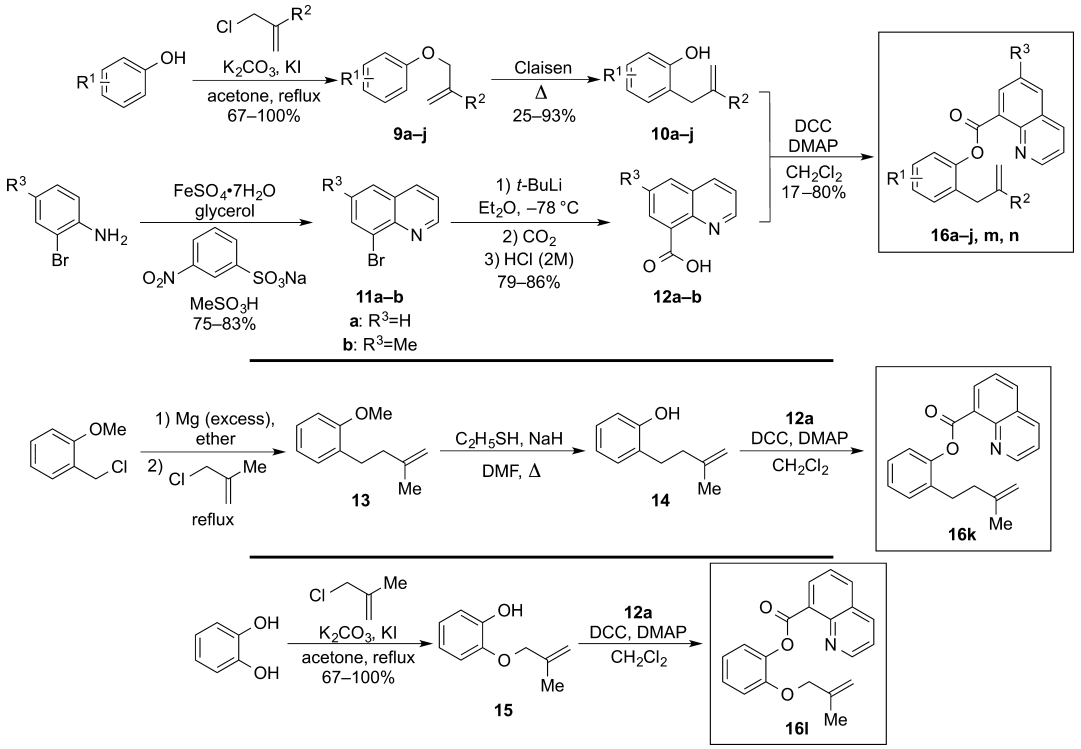
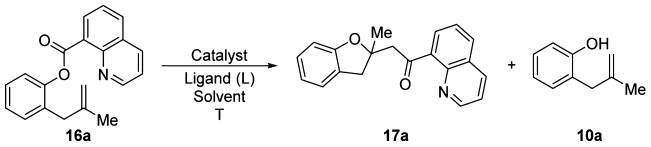


Table 1. Initial Optimization for Alkene Oxyacylation



entry	catalyst	L	sol.	temp (°C)	yield of **17a** (**10a**)
1	$Rh(PPh_3)_3Cl$		PhMe	130	
2	$[Rh(C_2H_4)_2Cl]_2$		PhMe	130	
3	$Rh(cod)_2OTf$		PhMe	130	20% (37%)[b]
4	$Rh(cod)_2BF_4$		DCE	110	40% (40%)[b]
5	$Rh(cod)_2OTf$		DCE	110	complex mixture
6	$Rh(cod)_2BF_4$	dppe	DCE	130	
7	$Rh(cod)_2BF_4$	dppb	DCE	130	40%[b]
8	$Rh(cod)_2BF_4$	dppp	DCE	130	82%[c]
9	$Rh(cod)_2BF_4$	dppp	DCE	90	25% (25%)[b]
10	$Rh(cod)_2BF_4$	dppp	DCE	110	65% (32%)[b]
11[d]	$Rh(cod)_2BF_4$	dppp	DCE/ PhMe	150	85%[c]

[a]Entries 1–5: Rh catalyst 20 mol%, 0.1 M **16a**, 24 h, entries 6–11: $Rh(cod)_2BF_4$ (10 mol%), ligand (12 mol %), 0.05 M **16a**, 24 h. [b]Determined by ^1H NMR spectroscopy. [c]Yield after chromatography. [d]Conditions used for further substrate evaluation. Legend: dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphino)-propane, dppb = 1,4-bis(diphenylphosphino)butane, DCE = 1,2-dichloroethane.

toluene and DCE (8:2) was chosen since it provided homogeneous reactions with a wider variety of substrates than DCE alone.

Substrate Scope Studies. Using the optimized conditions, we examined the scope of the oxyacylation reaction of alkenes (Table 2). Both electron-donating and electron-withdrawing substituents on the aromatic linker gave oxyacylation products in good yields (Entries 1–6), although substrates bearing electron donating groups *para* to the phenolic oxygen required longer reaction times (Entries 1 and 2). In the presence of another ester group, acyl C–O bond activation occurred exclusively at the 8-quinoline carboxylate ester, leaving the other ester untouched (Entry 4). Substitution at the 6-position of the aromatic linker improved the product to byproduct ratio. We reasoned that the restricted rotation of the acyl group forced the reacting ester group closer to the alkene, facilitating the oxyacylation reaction (Entries 5 and 6). A brief screen of the alkene moiety indicated a substituent is required for oxyacylation to occur. We did not observe any oxyacylation product **17h** when R = H (**16h**), possibly due to facile β-hydride elimination or alkene isomerization to the styrenyl position (Entry 7). Substituting with ethyl and methyl benzyl ether groups provided products in good yield (Entries 8 and 9). Extending the alkene tether produced chroman **17k** from **16k** (Entry 10). For allylic ether **16l**, we observed oxyacylation at 130 °C (Entry 11), but at higher temperatures (150 °C) the substrate predominantly underwent a Claisen rearrangement. Substitution on the 6-position of the quinoline directing group in **16m** and **16n** enabled the synthesis of **17m** and **17n** in slightly diminished yields relative to congeners **17a** and **17f** (Entries 12 and 13). We accomplished the oxyacylation reaction of **16n** on larger scale (0.75 mmol of **16n**), providing a better yield of **17n** (88%) than a smaller scale reaction (Entry13). Substrates without an aryl linkage between the ester and alkene did not produce detectable quantities of oxyacylation products under the standard oxyacylation conditions. Our attempt at an oxyacylation reaction of a substrate without a directing group was unsuccessful.[23]

Mechanistic Studies of Alkene Oxyacylation. Reaction optimization and mechanistic studies focused on substrate **16f** due to its clean conversion to product and incorporation of a

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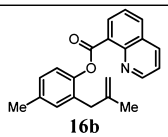
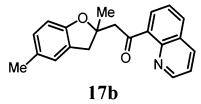
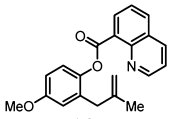
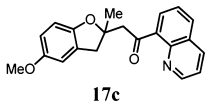
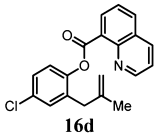
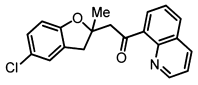
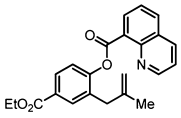
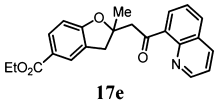
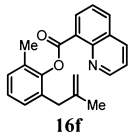
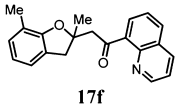
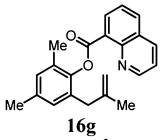
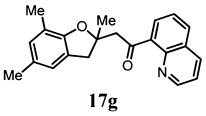
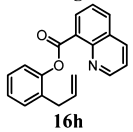
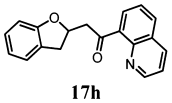
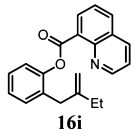
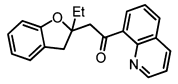
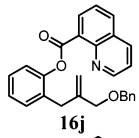
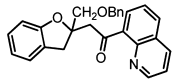
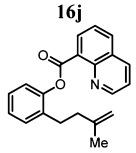
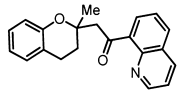
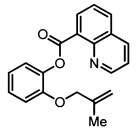
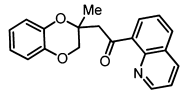
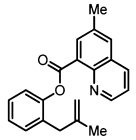
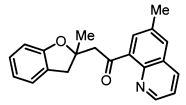
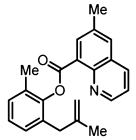
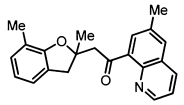
Table 2. Reaction Scope for Alkene Oxyacylation

Entry	Substrate	Product	Yield [b]
1 [c]	 **16b**	 **17b**	79%
2 [c]	 **16c**	 **17c**	60%[d]
3	 **16d**	 **17d**	65%
4	 **16e**	 **17e**	78%
5	 **16f**	 **17f**	90% 76%[f]
6	 **16g**	 **17g**	81%
7	 **16h**	 **17h**	--
8	 **16i**	 **17i**	78%
9	 **16j**	 **17j**	51%
10	 **16k**	 **17k**	85%
11	 **16l**	 **17l**	25%[e]
12	 **16m**	 **17m**	72%[f]
13	 **16n**	 **17n**	78%[f] 88%[g]

[a]Conditions: substrate (0.1 mmol), $Rh(cod)_2BF_4$ (10 mol%), dppp (12 mol%), PhMe/DCE = 8:2, 150 °C, 24 h. [b]Yield after chromatography [c]36 h. [d]70% brsm. [e]130 °C, 50% brsm. [f]Conditions: substrate (0.3 mmol), $Rh(cod)_2BF_4$ (10 mol%), dppp (12 mol%), PhMe/DCE = 8:2, 150 °C, 24 h. [g]Substrate (0.238 g, 0.75 mmol), $Rh(cod)_2BF_4$ (10 mol%), dppp (12 mol%), PhMe/DCE = 8:2, 150 °C, 24 h.

methyl group that we use as a diagnostic NMR reporting signal (see below, Table 3). Reactions were heated for 60 min over a range of temperatures from 90 to 150 °C (Entries 1–4); no product formation was observed at 90 °C while the reaction at 150 °C gave optimal conversion. Also, the short reaction time under the optimized conditions made obtaining quantitative initial rate kinetics challenging. Catalyst loadings were examined from 1 to 10 mol% (Entries 1, 5–8); however, conversion diminished below 5 mol% (Entries 6 and 8). A longer reaction time (48 h) with 2 mol% catalyst loading led to increased formation of the byproduct **10f** without significantly improving the yield of **17f** (Entry 7). Variation in the ligand loading with respect to rhodium revealed that a slight excess of ligand was necessary for success (Entries 5, 9, and 10). A 2:1 dppp:Rh ratio gave only a trace amount (<1%) of product and the NMR showed >95% of starting material **16f** remaining (Entry 10). Optimal conversion occurred in 5 min at 150 °C with 10 mol% catalyst and 12 mol% ligand, providing **17f** in 95% isolated yield with minimal formation of **10f** (Entries 11 and 12).

To begin our examination of the oxyacylation mechanism, we investigated the structure of the catalyst formed by mixing stoichiometric $Rh(cod)_2BF_4$ and dppp. The reaction of one equivalent of $[Rh(cod)_2]BF_4$ with 1.2 equiv of dppp resulted in two product signals by ^{31}P NMR. The major product signal at 10.55 ppm (doublet, J_{Rh-P} = 140 Hz) we assign to $[Rh(cod)dppp]^+$, while the minor product signal observed at 8.29 ppm (doublet, J_{Rh-P} = 130 Hz) we assign to $[Rh(dppp)_2]^+$. The assignment of these NMR signals is in good agreement with literature data for similar compounds.[24−27] When we allowed 2 equiv of dppp to react with $[Rh(cod)_2]BF_4$, we observed only $[Rh(dppp)_2]^+$ and free dppp by ^{31}P NMR. Re-examining the results from experiments with varied ligand loading, we obtained less than optimal results when 0.5 equiv or 2 equiv of dppp were used (Table 3, Entries 5, 9, and 10). A slight excess of dppp gave the best results. These results, along with the ^{31}P NMR data suggest that the active catalyst has one dppp ligand coordinated.

We performed crossover experiments to determine whether the mechanism involved inter- or intramolecular steps. We subjected substrates **16f** and **16m** to standard reaction conditions in a single pot. After 24 h, we observed all four possible products (Table 4, Entry 1), confirming that intermolecular steps occur in alkene oxyacylation. Moreover, complete crossover occurs in 5 min, which is approximately the time the reaction takes to reach completion (Entry 2). This

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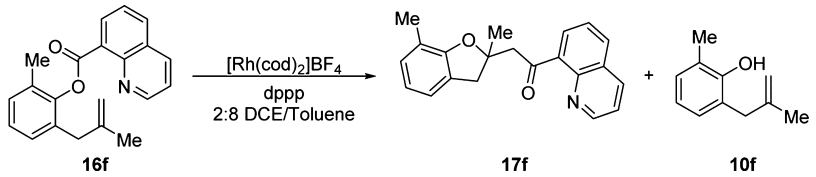
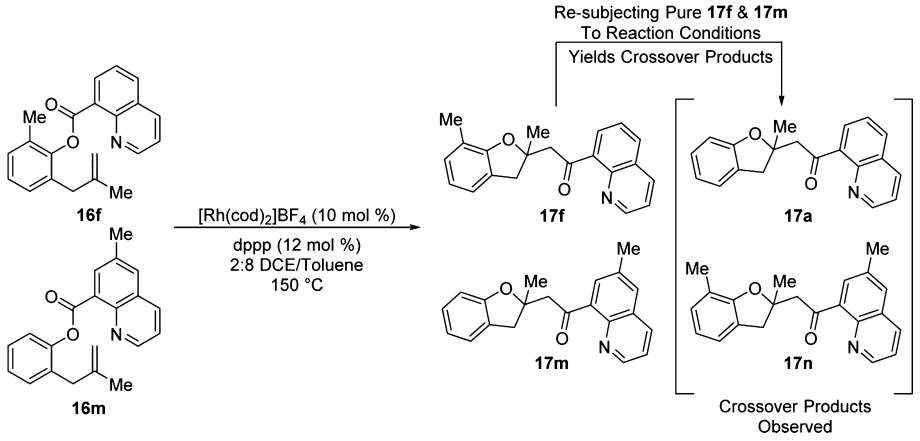
Table 3. Temperature, Catalyst, and Ligand Loading Optimization for Alkene Oxyacylation



					NMR ratios	
entry	catalyst loading (mol%)	ligand loading (mol%)	temp (°C)	time (min)	**17f** (**10f**)	**16f**
1	10	12	150	60	>95% (2%)	0%
2	10	12	130	60	>95% (1%)	2%
3	10	12	110	60	87% (2%)	11%
4	10	12	90	60	0% (5%)	95%
5	5	6	150	60	91% (7%)	2%
6	3	3.6	150	60	52% (2%)	46%
7	2	2.4	150	48 h	31%(15%)	54%
8	1	1.2	150	60	1% (0%)	>95%
9	5	2.5	130	60	15%(0%)	85%
10	5	10	130	60	<1%(0%)	>95%
11	10	12	150	5	>95% (0%)	2%
12	10	12	150	5	95%[a](0%)	2%

[a]Isolated yield after chromatography.

Table 4. Crossover Reactions



				NMR product ratios			
entry	description	starting materials	time	**17a**	**17f**	**17m**	**17n**
1	starting material crossover	**16f, 16m**	24 h[a]	23%	28%	26%	23%
2	starting material crossover	**16f, 16m**	5 min[a]	24%	24%	30%	22%
3	product crossover	**17f, 17m**	5 min	11%	40%	35%	14%
4	product crossover	**17f, 17m**	24 h	17%	33%	29%	21%
5	starting material crossover	**16f, 16m**	1 h[b]	16%	14%	48%	22%
6	starting material; no cat.	**16f, 16m**	24 h	no reaction, no crossover			
7	product; no cat.	**17f, 17m**	24 h	no reaction, no crossover			

[a]Full conversion of starting materials. [b]Reaction heated to 130 °C, yield of all products was 74% with 23% of unchanged **16f** recovered.

indicates that most of the crossover in alkene oxyacylation occurs during the initial formation of products, not through reactivation and crossover after oxyacylation. Independently subjecting purified products **17f** and **17m** to the reaction conditions also provided a mixture of **17a**, **17f**, **17m**, and **17n** (Entries 3 and 4), although not in the same ratio as obtained when we performed crossover starting with esters **16f** and **16m** in entries 1 and 2. After we allowed equimolar amounts of **17f** and **17m** to react for 5 min (Entry 3), the ratio of ketones was 11:40:35:14 (**17a**:**17f**:**17m**:**17n**), which is skewed toward the starting ketone pair. After we allowed **17f** and **17m** to react for 24 h (Entry 4), the ratio of ketones was 17:33:29:21 (**17a**:**17f**:**17m**:**17n**), which is closer to the ratio obtained in the crossover experiments initiated with esters **16f** and **16m**. These results suggest that the qualitative rate at which crossover occurs in the products was slower than rate of crossover when beginning with esters. Re-isolation of starting materials after 1 h of heating to 130 °C confirmed that crossover of the starting esters does not occur (Entry 5). Control reactions confirmed the need for rhodium in the

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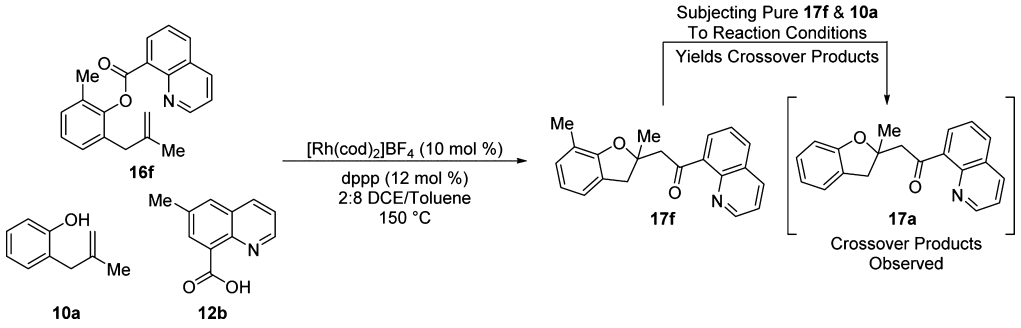
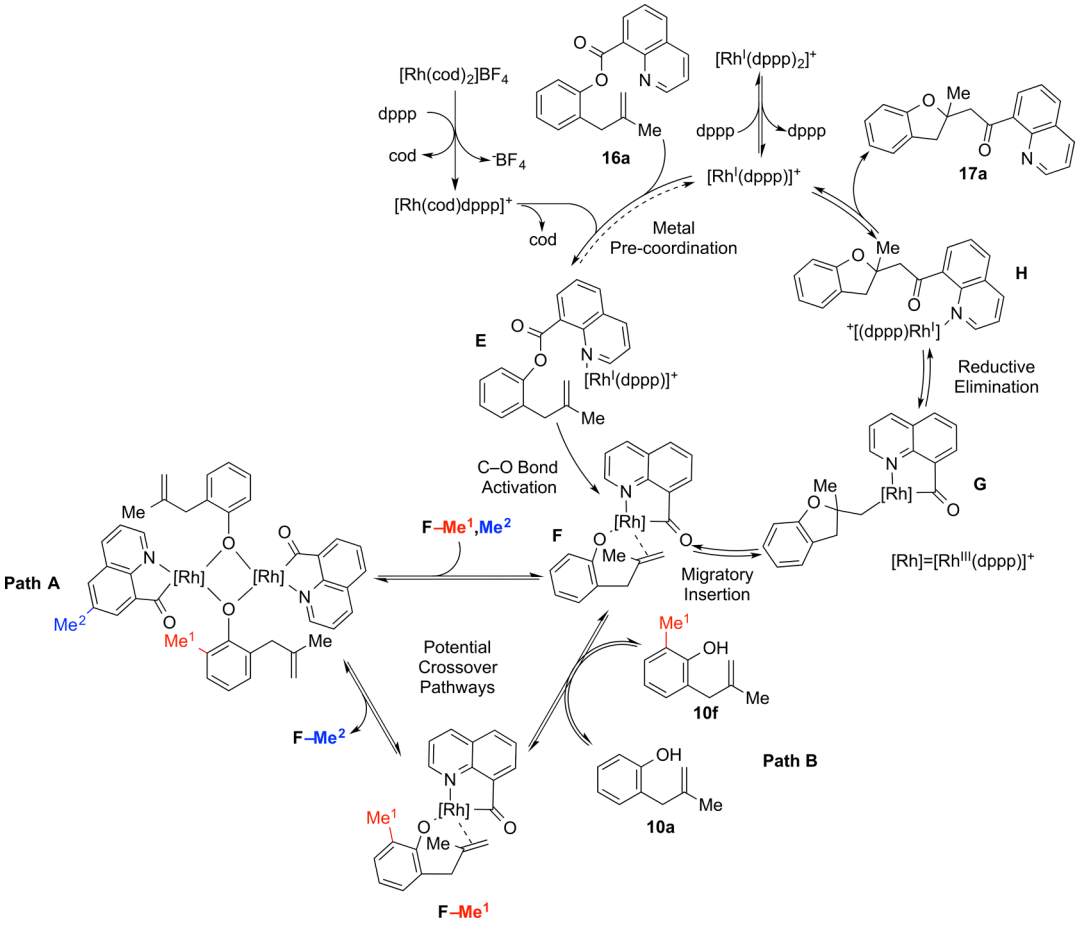
Table 5. Partial Crossover Reaction



				NMR product ratios		NMR phenol ratios	
entry	description	starting materials	time	**17a**	**17f**	**10a**	**10f**
1	starting material crossover	**16f, 10a**	1 h	53%	47%	60%	40%
2	product crossover	**17f, 10a**	1 h	28%	72%	64%	36%
3	starting material crossover	**16f, 12b**	12 h	no reaction			
4	product crossover	**17m, 12b**	12 h	no reaction			
5	starting material; no cat.	**16f, 10a**	12 h	no reaction			
6	product; no cat.	**17f, 10a**	12 h	no reaction			

Scheme 7. Alkene Oxyacylation Mechanism



crossover reaction as well as the alkene oxyacylation reaction (Entries 6 and 7). Notably, we did not observe esters **16a** or **16n** in the reaction mixture from entry 6, indicating transesterification of the starting materials is not the cause of crossover. The results in Table 4 indicate that the crossover event is catalyst mediated and that activation of the products by the catalyst is also possible. This suggests that the reaction mechanism contains reversible steps, and the product, through interaction with the catalyst, can proceed back to an intermediate capable of crossover.

After observing complete crossover above, as well as noting the formation of phenol **10a** and **10f** (Table 1), we sought to determine if independent fragments were able to intercept crossover events by examining partial crossover reactions

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(Table 5). After subjection of starting material **16f** and phenol **10a** to oxyacylation reaction conditions, we observed products **17a** and **17f** along with phenols **10a** and **10f** (Table 5, Entry 1). This indicates that an exogenous phenol can intercept the catalytic intermediates capable of crossover. Furthermore, when purified **17f** was resubjected to the reaction conditions with phenol **10a**, we observed crossover product **17a** (Entry 2). We attempted partial crossover reactions with carboxylic acid **12b** but did not observe **17a** or **17f** (Entries 3 and 4). This result indicates that **12b** is not a viable reactive intermediate, nor is **12b** capable of intercepting reactive intermediates by crossover. Control reactions for the partial crossover experiments further confirmed the need for rhodium in the crossover reaction and that background transesterification does not occur in the presence of **10a** (Entries 5 and 6).

These results are in contrast to Johnson's findings on the related intramolecular carboacylation reaction of 8-acyl quinoline ketones. When studying the mechanism of alkene carboacylation, Johnson and co-workers did not observe any crossover products, indicating that the intermediates were short-lived and could not undergo intermolecular exchange during catalysis. We observed crossover from alkene oxyacylation reactions, indicating that the intermediates survive long enough to undergo intermolecular exchange.

Based on these findings, we postulate that the alkene oxyacylation mechanism begins with $[Rh(cod)_2]BF_4$ performing a ligand exchange with dppp (Scheme 7). The $[Rh(cod)\text{-}dppp]^+$ complex then enters the catalytic cycle through dissociation of COD and coordination with substrate **16a** (intermediate **E**). Carbon−oxygen bond activation occurs next; this step is believed to be irreversible due to the lack of observed crossover between starting materials. We suggest that the crossover event occurs at intermediate **F**. Substitution, of phenoxide ligands at intermediate **F** is consistent with our crossover and partial crossover experiments. (Table 5, Entry 1). We propose two possible mechanisms for this crossover event. Intermediate **F** could exchange an alkoxide ligand by associative or dissociative substitution with phenol **10f**. Alternatively, intermediate **F** may associate with analogous intermediate **F**−**Me**^{1}, **Me**^{2} to form a bimetallic intermediate with bridging alkoxide ligands. Dissociation of the bridging alkoxides to form intermediates **F**−**Me**^{1} and **F**−**Me**^{2} would then explain crossover. We cannot distinguish between these cross over mechanisms at this time. Intermediate **F** then undergoes migratory insertion across the alkene tether followed by reductive elimination to afford intermediate **H**. The catalyst dissociates from the directing group to produce product **17a**. Reverse arrows are drawn from intermediate **F** to product **17a** to rationalize the crossover observed when the products **17** were re-subjected to the catalyst.

CONCLUSION

While our efforts toward ketone carboacylation have yet to come to fruition, this research paved the way to our discovery of alkene oxyacylation. Isolation of alcohol **8** suggested to us that carbon−carbon bond activation and migratory insertion across a ketone occurred readily, but reductive elimination may not be favorable. We hypothesized that if reductive elimination to form the ester functional group is unfavorable, then the reverse, oxidative addition into an ester, could be utilized in alkene addition reactions. The alkene oxyacylation using esters proved to be effective and efficient, validating this hypothesis. Moreover, we have found the reaction is rapid and can be complete within 5 min, providing isolated yields as high as 95%. Mechanistic studies provided insight into the intermolecular nature of the reaction, which allowed us to map the reversible steps in the catalytic cycle through crossover studies.

EXPERIMENTAL DETAILS

All reactions were carried out using flame-dried glassware under a nitrogen or argon atmosphere unless aqueous solutions were employed as reagents. Tetrahydrofuran (THF) was dried by distillation from benzophenone/sodium. Dichloromethane (CH_2Cl_2) and isopropanol were degassed by bubbling a stream of argon through the liquid in a Schlenk flask then stored and used in a N_2-filled glovebox. All other chemicals were used as received. Analytical thin layer chromatography (TLC) was carried out using 0.25 mm silica plates. Eluted plates were visualized with UV light. Flash chromatography was performed using 230−400 mesh (particle size 0.04−0.063 mm) silica gel.

^{1}H NMR (300 and 500 MHz) and ^{13}C NMR (75 and 125 MHz) spectra were obtained on FT NMR instruments. NMR spectra were reported as δ values in ppm relative to chloroform or TMS for ^{1}H (7.26 and 0.00 ppm respectively), chloroform for ^{13}C (77.16 ppm). ^{1}H and ^{13}C NMR coupling constants are reported in Hz; multiplicity was indicated as follows; s (singlet); d (doublet); t (triplet); q (quartet); quint (quintet); m (multiplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dddd (doublet of doublet of doublet of doublets); dt (doublet of triplets); td (triplet of doublets); ddt (doublet of doublet of triplets); app (apparent); br (broad). Infrared (IR) spectra were obtained as films from CH_2Cl_2. High-resolution mass spectra (HRMS) in EI experiments were performed on a GC-MS system and ESI experiments were performed on a TOF instrument.

Phenol **3** was synthesized according to a published procedure.[4]

(2-Hydroxyphenyl)(quinolin-8-yl)methanone (3). White solid; ^{1}H NMR(500 MHz, $CDCl_3$) δ 12.30 (s, 1H, D_2O exchange), 8.90 (dd, J = 4.2, 1.8 Hz, 1H), 8.24 (dd, J = 8.4, 1.7 Hz, 1H), 7.99 (dd, J = 8.2, 1.4 Hz, 1H), 7.72 (dd, J = 7.0, 1.5 Hz, 1H), 7.65 (t, J = 8.1 Hz, 1H), 7.49−7.44 (m, 2H), 7.15 (dd, J = 8.0, 1.7 Hz, 1H), 7.07 (d, J = 8.5 Hz, 1H), 6.70 (ddd, 8.3, 7.2, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7, 163.1, 151.3, 145.9, 137.9, 136.8, 136.2, 134.1, 130.1, 128.4, 128.3, 125.9, 122.0, 120.9, 118.9, 118.4; HRMS (ESI) calcd for $C_{16}H_{11}NO_2$ $[M+Na]^+$ m/z 272.0682, found 272.0688.

1-Phenyl-2-(2-(quinoline-8-carbonyl)phenoxy)ethan-1-one (1a) and (3-Hydroxy-3-(quinolin-8-yl)-2,3-dihydrobenzofuran-2-yl)(phenyl)methanone (2a). NaH (23 mg, 0.095 mmol) was added to a solution of 2-hydroxyphenyl 8-quinolinyl ketone **3** (0.249 g, 1 mmol) in DMF (4 mL) at 0 °C, the mixture was stirred for 10 min. Potassium iodide (0.166 g, 1 mmol) and 2-bromoacetophenone (0.4 g, 2 mmol) were added. The formation of products was monitored by TLC. After 2 h, NH_4Cl (sat.) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with 2 M LiCl (2 × 20 mL), brine, dried over Na_2SO_4, and concentrated. The crude mixture was purified by flash column chromatography to provide **1a** (185 mg, 0.5 mmol, 50%) and the aldol product **2a** (113 mg, 0.31 mmol, 31%). 10% of the starting material remained as determined by ^{1}H NMR of the crude mixture.

1-Phenyl-2-(2-(quinoline-8-carbonyl)phenoxy)ethanone (1a). Yellow solid (185 mg, 0.5 mmol, 50%); R_f = 0.21 (40% EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (dd, J = 4.2, 1.8 Hz, 1H), 8.06 (dd, J = 8.3, 1.7 Hz, 1H), 7.86 (dd, J = 7.7, 1.3 Hz, 1H), 7.77 (dd, J = 8.2, 1.3 Hz, 1H), 7.75 (dd, J = 7.1, 1.4 Hz, 1H), 7.61 (dd, J = 8.3, 1.2 Hz, 2H), 7.53−7.47 (m, 1H), 7.47−7.40 (m, 2H), 7.35−7.28 (m, 3H), 7.08 (app td, J = 7.5, 0.9 Hz, 1H) 6.81 (d, J = 8.4 Hz, 1H), 4.71 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 193.7, 157.6, 150.4, 145.8, 141.1, 135.9, 134.0, 133.8, 133.7, 131.4, 130.2, 130.0, 128.63, 128.59, 128.2, 127.8, 125.9, 121.9, 121.3, 114.1 72.1; IR (film) 3064, 2922, 1701, 1646, 1595, 1451, 1291, 1215 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{17}NO_3$ $[M+Na]^+$ m/z 390.1101, found 390.1118.

(3-Hydroxy-3-(quinolin-8-yl)-2,3-dihydrobenzofuran-2-yl)-(phenyl)methanone (2a). White solid (113 mg, 0.31 mmol, 31%); R_f = 0.38 (40% EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (s,

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1H, D_2O exchange), 8.48 (dd, J = 4.3, 1.8 Hz, 1H), 8.24 (dd, J = 8.4, 1.8 Hz, 1H), 7.81 (dd, J = 8.2, 1.3 Hz, 1H), 7.75 (dd, J = 8.4, 1.9 Hz, 2H), 7.50 (app t, J = 7.4 Hz, 1H), 7.46−7.34 (m, 4H), 7.29−7.22 (m, 3H), 7.11 (d, J = 8.1 Hz, 1H), 7.03 (app td, J = 7.5, 0.9 Hz, 1H) 5.94 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2, 159.9, 147.5, 146.4, 139.4, 137.6, 137.2, 132.9, 131.8, 130.7, 129.6, 129.1,[28] 129.0, 128.4, 128.1, 126.8, 125.7, 122.2, 121.1, 110.8, 94.9, 88.6; IR (film) 3414, 3057, 1695, 1598, 1476, 1226 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{17}NO_3$ $[M+Na]^+$ m/z 390.1101, found 390.1099.

1-(2-(Quinoline-8-carbonyl)phenoxy)propan-2-one (1b) and 1-(3-Hydroxy-3-(quinolin-8-yl)-2,3-dihydrobenzofuran-2-yl)-ethanone (2b). NaH (23 mg, 0.95 mmol) was added to a solution of 2-hydroxyphenyl 8-quinolinyl ketone **3** (0.249 g, 1 mmol) in DMF (4 mL) at 0 °C, the mixture was stirred for 10 min. Potassium iodide (0.166 g, 1 mmol) and chloroacetone (0.32 mL, 4 mmol) were added. The formation of products was monitored by TLC. After 4 h, NH_4Cl (sat.) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with 2 M LiCl (2 × 20 mL), brine, dried over Na_2SO_4 and concentrated. The crude mixture was purified by flash column chromatography to give **1b** (87 mg, 0.28 mmol, 28%), starting material **3** (158 mg, 0.63 mmol, 63%), and trace amounts of aldol **2b**.

1-(2-(Quinoline-8-carbonyl)phenoxy)propan-2-one (1b). Yellow solid (87 mg, 0.28 mmol, 28%); R_f = 0.16 (40% EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (dd, J = 4.1, 1.5 Hz, 1H), 8.15 (dd, J = 8.3, 1.4 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.85 (d, J = 7.1 Hz, 1H), 7.79 (dd, J = 7.7, 1.4 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 8.4 Hz, 1H), 7.36 (dd, J = 8.3, 4.2 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 4.11 (s, 2H), 1.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 196.3, 156.7, 150.6, 145.8, 140.6, 135.9, 133.6, 131.6, 130.4, 130.0, 128.9, 128.0, 125.9, 121.6, 121.4, 112.8, 73.5, 26.0; IR (film) 3068, 2922, 1721, 1661, 1595, 1451, 1294, 1266 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{15}NO_3$ $[M+Na]^+$ m/z 328.0944, found 328.0955.

1-(3-Hydroxy-3-(quinolin-8-yl)-2,3-dihydrobenzofuran-2-yl)-ethanone (2b). White solid; R_f = 0.42 (40% EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.98 (s, 1H, D_2O exchange), 8.88 (dd, J = 4.3, 1.8 Hz, 1H), 8.27 (dd, J = 8.4, 1.7 Hz, 1H), 7.78 (dd, J = 8.2, 1.1 Hz, 1H), 7.51 (dd, J = 8.4, 4.3 Hz, 1H), 7.44 (app t, J = 7.5 Hz, 1H), 7.39 (app td, J = 7.0, 1.4 Hz, 1H), 7.30 (dd, J = 7.5, 0.8 Hz, 1H), 7.14 (dd, J = 7.4, 1.3 Hz, 1H), 7.08−7.04 (m, 2H), 4.95 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 159.8, 148.0, 146.2, 139.6, 137.8, 131.4, 130.8, 129.3, 129.1, 128.3, 126.6, 125.9, 122.3, 121.4, 110.7, 97.2, 88.0, 27.9; IR (film) 3420, 3048, 2963, 2922, 2849, 1716, 1599, 1475 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{15}NO_3$ $[M+Na]^+$ m/z 328.0944, found 328.0944.

Synthesis of Complex 5. Wilkinson catalyst (0.409 g, 0.442 mmol) was added to a solution of 1-(2-(quinoline-8-carbonyl)-phenoxy)propan-2-one **1b** (0.135 g, 0.442 mmol) in dichloromethane (4 mL), The mixture was stirred at room temperature for 4 h and product formation was monitored by TLC. The mixture was concentrated and purified by gradient flash chromatography (20% EtOAc:Hex to 100% EtOAc). Recrystallization in EtOAc and pentane gave **5** as a brown solid (0.396 g, 0.409 mmol, 93% yield) which was stored at −20 °C. Attempts to remove small amounts of residual solvent led to decomposition.

Rhodium(III) Complex (5). Brown solid (0.396 g, 0.409 mmol, 93%); R_f = 0.35 (20% EtOAc in Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00−8.98 (m, 1H), 7.86 (d, J = 7.3 Hz, 1H), 7.69−6.77 (m, 37H), 6.51−6.48 (m, 1H), 4.32 (d, J = 15.7 Hz, 1H), 3.96 (d, J = 15.7 Hz, 1H), 1.24 (s, 3H); ^{13}C NMR[29] (125 MHz, $CDCl_3$) δ 207.6, 157.6, 156.0, 142.7, 142.5, 138.6, 136.7, 136.7, 136.1, 136.0, 135.6, 135.6, 134.8 (br), 133.6, 130.7, 129.8, 129.2, 129.1, 129.1, 128.6, 128.0, 128.0, 127.7, 127.6, 127.4, 127.2, 127.1, 127.0, 126.9, 126.0, 125.9, 121.7, 119.5, 117.9, 106.3 (d, J_{Rh-C} = 3.9), 77.0, 26.5; ^{31}P NMR (202 MHz, $CDCl_3$) δ 13.34 (dd, J_{Rh-P} = 128.1, J_{P-P} = 32.1 Hz), 10.94 (dd, J_{Rh-P} = 114.8, J_{P-P} = 32.1 Hz); IR (film) 3055, 1714, 1483, 1435, 1191, 1118 cm^{-1}; HRMS[30] (ESI) calcd for $C_{55}H_{45}ClNO_5P_2Rh$ $[M+Na]^+$ m/z 1022.1409, found 1022.1408; DEPT; COSY; HMBC; HMQC; The structure was confirmed by single crystal X-ray crystallography.

Attempted carboacylation reaction of **1a** with $[Rh(C_2H_4)_2Cl]_2$. In a nitrogen filled glovebox, a 1-dram reaction vial (polytetrafluoroethylene cap) was charged with $[Rh(C_2H_4)_2Cl]_2$ (0.0518 g, 0.133 mmol, 0.5 equiv), phenyl ketone **1a** (0.0980 g, 0.267 mmol), and toluene (2.67 mL). The reaction mixture was maintained at 90 °C for 24 h. The mixture was then removed from the glovebox, filtered through Celite , and concentrated to give a crude brown residue (0.0983 g). The crude product was purified by flash column chromatography (20% EtOAc in hexanes). Two products were isolated: alkene **6a** (0.0225 g, 0.0944 mmol, 35%) and alcohol **8a** (0.0042 g, 0.020 mmol, 7%).

1-Phenyl-2-(2-vinylphenoxy)ethanone (6a). Colorless solid (22.5 mg, 0.0944 mmol, 37%); R_f = 0.47 (20% EtOAc in Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02−8.00 (m, 2H), 7.62 (dddd, J = 6.9, 6.9, 1.3, 1.3 Hz, 1H), 7.52−7.49 (m, 3H), 7.22−7.18 (m, 1H), 7.14 (dd, J = 17.8, 11.2 Hz, 1H), 6.98 (app t, J = 7.3 Hz, 1H), 6.81 (dd, J = 8.3, 0.8 Hz, 1H), 5.80 (dd, J = 17.8, 1.5 Hz, 1H), 5.31−5.28 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.6, 155.3, 134.7, 134.0, 131.5, 129.0, 128.9, 128.3, 127.5, 127.0, 121.8, 115.2, 112.5, 71.5; IR (thin film, CH_2Cl_2) 3064, 3032, 2916, 1703, 1625, 1598 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{14}O_2$ $[M+Na]^+$ m/z 261.0886, found 261.0891.

3-Phenyl-2,3-dihydrobenzofuran-3-ol (8a). Colorless oil (4.2 mg, 0.020 mmol, 8%); R_f = 0.41 (20% EtOAc in Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2H), 7.39−7.36 (m, 2H), 7.33−7.29 (m, 2H), 7.11 (app d, J = 7.5 Hz, 1H), 6.98−6.94 (m, 2H), 4.71 (d, J = 10.3 Hz, 1H), 4.51 (d, J = 10.3 Hz, 1H), 2.29 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 142.7, 132.3, 130.8, 128.4, 127.7, 126.2, 124.5, 121.6, 110.9, 86.3, 82.7; IR (thin film, CH_2Cl_2) 3440, 3058, 3030, 2946, 1599 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{12}O_2$ $[M+Na]^+$ m/z 235.0730, found 235.0731.

Following the general procedure above using methyl ketone **1b** (0.1000 g. 0.328 mmol, 1 equiv), three products were isolated: alkene **6b** (0.0202 g, 0.115 mmol, 35%), *trans*-alkene **7b** (0.0013 g, 0.0086 mmol, 3%), and alcohol **8b** (0.0010 g, 0.0048 mmol, 2%)

1-(2-Vinylphenoxy)propan-2-one (6b). Colorless oil (20.2 mg, 0.1146 mmol, 35%); R_f = 0.35 (20% EtOAc in Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, J = 7.6, 1.5 Hz, 1H), 7.22 (dt, J = 7.8, 1.6 Hz, 1H), 7.13 (dd, J = 17.8, 11.2 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 5.79 (dd, J = 17.8, 1.2 Hz, 1H), 5.32 (dd, J = 11.2, 1.2 Hz, 1H), 4.54 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 154.9, 131.2, 129.1, 127.2, 126.9, 121.9, 115.2, 111.9, 73.5, 27.0; IR (thin film, CH_2Cl_2) 3061, 3036, 3021, 2981, 2958, 2916, 2848, 1737, 1720, 1626, 1599, 1577 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{12}O_2$ $[M+Na]^+$ m/z 199.0730, found 199.0760.

***(E)*-1-(2-(But-1-en-1-yl)phenoxy)propan-2-one (7b).** Colorless oil (1.0 mg, 0.0049 mmol, 2%); R_f = 0.58 (20% EtOAc in Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, J = 7.7, 1.5 Hz, 1H), 7.15 (dt, J = 9.0, 1.6 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.76 (d, J = 16.0 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H), 6.30 (ddd, J = 16.0, 6.5, 6.5 Hz, 1H), 4.54 (s, 2H), 2.32 (s, 2H), 2.30−2.27 (m, 2H), 1.14 (t, J = 7.5 Hz, 3H);); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.5, 154.5, 134.1, 128.0, 127.6, 126.8, 123.0, 121.9, 111.9, 73.6, 27.0, 26.6, 13.8; COSY; IR (thin film, CH_2Cl_2) 2963, 2919, 2873, 2849, 1723, 1598, 1579 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{16}O_2$ $[M+Na]^+$ m/z 227.1043, found 227.1065.

3-Methyl-2,3-dihydrobenzofuran-3-ol (8b).[31] Colorless oil (1.3 mg, 0.0087 mmol, 3%); R_f = 0.28 (20% EtOAc in Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 7.4 Hz, 1H), 7.27−7.24 (m, 1H), 6.96 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 4.50 (d, J = 10.1 Hz, 1H), 4.31 (d, J = 10.0 Hz, 1H), 1.96 (s, 1H), 1.69 (s, 3H); IR (thin film, CH_2Cl_2) 3385 (br), 2969, 2917, 1610, 1600, 1479, 1465 cm^{-1}; HRMS (EI) calcd for $C_9H_{10}O_2$ $[M]^+$ m/z 150.0675, found 150.0676.

Overall Scheme for the Synthesis of Ester Substrates. The substrates **16a** through **16l** for the oxyacylation reaction were synthesized according to literature procedure.[12,32] Oxyacylation reactions to form products **17a** to **17l** are also reported previously reported in literature.[12,32]

Synthesis of 6-Methylquinoline-8-carboxylic Acid. 8-Bromo-6-methylquinoline (1.63 g, 7.3 mmol) and dry ether (30 mL) were added to a flame-dried 3-necked 50 mL round-bottom flask under N_2.

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The mixture was cooled to −78 °C then *t*-Bu Li (1.7 M) in pentane (8.6 mL, 14.6 mmol) was added over 20 min. The mixture was maintained at −78 °C for 10 min and then poured into a 1 L beaker containing dry ice. After all remaining dry ice had sublimed, aqueous HCl (1 M) was added until the reaction mixture became acidic (pH = 3). The mixture was extracted with chloroform (10 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was further purified by high vacuum (>0.1 mmHg) at a temperature of 100 °C to yield 6-methylquinoline-8-carboxylic acid **12b** (1.082 g, 5.79 mmol, 79%).

6-Methylquinoline-8-carboxylic Acid (12b). Tan solid (1.082 g, 5.79 mmol, 79%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.63 (br s, 1H) 8.83 (dd, J = 4.5, 1.7 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.32 (dd, J = 8.4, 1.7 Hz, 1H), 7.85 (d, J = 0.9 Hz, 1H), 7.57 (dd, J = 8.4, 4.4 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ167.6, 147.6, 144.0, 138.1, 137.8, 137.5, 131.9, 128.5, 124.2, 121.8, 21.6; IR (film) 3426, 1640 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_9NO_2$ $[M+Na]^+$ m/z 210.0525, found 210.0524.

General Synthesis of Esters. In a flame-dried round-bottom flask, 8-quinolinecarboxylic acid **12** (1 equiv), *N*,*N*′-dicyclohexylcarbodiimine (1.5 equiv), 4-(dimethylamino)pyridine (1equiv), and phenol **10** (1−2 equiv) were dissolved in dichloromethane to generate a 0.1 M solution with respect to 8-quinolinecarboxylic acid **12**. The mixture was refluxed for 24 h. Insoluble byproducts were removed by vacuum filtration using fritted glass funnel. The filtrate was washed with saturated aqueous NH_4Cl twice, followed by a saturated $NaHCO_3$ wash. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The resulting crude product was purified by flash chromatography (gradient, EtOAc:Hex) to provide the product ester **16**.

2-(2-Methylallyl)phenyl 6-Methylquinoline-8-carboxylate (16m). yellow oil (388 mg, 1.223 mmol, 64%); R_f = 0.35 (20% EtOAc in Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (dd, J = 4.1, 1.6 Hz, 1H), 8.13 (dd, J = 8.2, 1.6 Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H), 7.77 (s, 1H), 7.44 (dd, J = 8.2, 4.1 Hz, 1H), 7.38 (m, 1H), 7.33 (m, 2H), 7.24 (m, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 3.53 (s, 2H), 2.61 (s, 3H), 1.74 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 150.7, 149.7, 144.5, 144.2, 135.6, 135.5, 133.0, 132.0, 130.8, 130.7, 130.6, 128.6, 127.4, 126.1, 122.8, 121.8, 112.3, 38.6, 22.5, 21.5; IR (thin film, CH_2Cl_2) 3085, 2972, 2925, 1750, 1650 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{19}NO_2$ $[M+H]^+$ m/z 318.1489, found 318.1489.

2-Methyl-6-(2-methylallyl)phenyl 6-Methylquinoline-8-carboxylate (16n). Yellow oil (354 mg, 1.068 mmol, 62%); R_f = 0.38 (20% EtOAc in Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (dd, J = 4.1, 1.5 Hz, 1H), 8.13−8.05 (m, 2H), 7.72 (s, 1H), 7.40 (dd, J = 8.2, 4.1 Hz, 1H), 7.24−7.15 (m, 3H), 4.87 (s, 1H), 4.76 (s, 1H), 3.60 (s, 2H), 2.58 (s, 3H), 2.46 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 150.5, 148.5, 144.3, 144.2, 135.5, 135.5, 132.7, 132.2, 131.0, 130.9, 130.6, 129.1, 128.5, 128.2, 125.9, 121.7, 112.2, 38.7, 22.4, 21.4, 17.0; IR (thin film, CH_2Cl_2) 3072, 3022, 2968, 2921, 2854, 1749, 1651, 1597 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{21}NO_2$ $[M+H]^+$ m/z 332.1645, found 332.1636.

General Alkene Oxyacylation Reaction. In a nitrogen filled glovebox, $Rh(cod)_2BF_4$ (0.01 mmol, 0.1 equiv), 1,3-bis(diphenylphosphoino)propane (0.012 mmol, 0.12 equiv), and DCE (0.4 mL) were added to a 1 dram reaction vial (polytetrafluoroethylene cap). The mixture was stirred at room temp for 1 h and then transferred to a 1 dram vial containing ester (0.1 mmol, 1 equiv) and toluene (1.6 mL). The reaction mixture was maintained at 150 °C for a specified amount of time. The mixture was then removed from the glovebox and concentrated. The crude product was purified by flash column chromatography (gradient, EtOAc:Hex) to afford the oxyacylation product.

2-(2-Methyl-2,3-dihydrobenzofuran-2-yl)-1-(6-methylquinolin-8-yl)ethanone (17m). Colorless oil (22 mg, 0.069 mmol, 69%); R_f = 0.49 (20% EtOAc in Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (dd, J = 4.2, 1.8 Hz, 1H), 8.07 (dd, J = 8.3, 1.8 Hz, 1H), 7.66 (s, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.37 (dd, J = 8.3, 4.2 Hz, 1H), 7.13 (dd, J = 7.3, 0.9 Hz, 1H), 7.05 (t, J = 2.3 Hz, 1H), 6.81 (td, J = 7.4, 0.9 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 3.98 (d, J = 16.4 Hz, 1H), 3.94 (d, J = 15.9 Hz, 1H), 3.44 (d, J = 15.9 Hz, 1H), 3.16 (d, J = 15.9 Hz, 1H), 2.50 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 158.5, 149.7, 144.3, 139.8, 136.1, 135.7, 131.5, 130.1, 128.5, 127.9, 127.4, 125.3, 121.5, 120.2, 109.4, 87.6, 54.8, 41.6, 27.1, 21.5; IR (thin film, CH_2Cl_2) 3048, 2970, 2929, 1682, 1596,1480, 1240 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{19}NO_2$ $[M+Na]^+$ m/z 340.1308, found 340.1309.

2-(2,7-Dimethyl-2,3-dihydrobenzofuran-2-yl)-1-(6-methylquinolin-8-yl)ethanone (17n). Colorless oil (26 mg, 0.078 mmol, 78%); R_f = 0.47 (20% EtOAc in Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (dd, J = 4.1, 1.6 Hz, 1H), 8.07 (dd, J = 8.3, 1.6 Hz, 1H), 7.64 (s, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.38 (m, 2H), 6.96 (d, J = 7.3 Hz, 1H), 6.84 (t, J = 7.5 Hz, 1H), 6.72 (t, J = 7.4 Hz, 1H), 4.01 (d, J = 15.3 Hz, 1H), 3.82 (d, J = 15.3 Hz, 1H), 3.44 (d, J = 15.9 Hz, 1H), 3.13 (d, J = 15.9 Hz, 1H), 2.46 (s, 3H), 1.86 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.0, 157.1, 149.7, 144.3, 140.1, 136.1, 135.6, 131.2, 129.8, 129.1, 128.4, 126.4, 122.6, 121.5, 120.0, 119.6, 87.1, 55.1, 41.7, 27.6, 21.5, 15.1; IR (thin film, CH_2Cl_2) 3050, 2970, 2920, 1682, 1597,1466, 1237 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{21}NO_2$ $[M+H]^+$ m/z 332.1645, found 332.1644. We obtained **17n** as a colorless oil (209.4 mg, 0.660 mmol, 88% yield) on larger scale reaction after purification by column chromatography (isocratic 15% EtOAc in Hex); the ^{1}H NMR matched that obtained from the smaller scale experiment.

Crossover Reactions. In a nitrogen filled glovebox, $Rh(cod)_2BF_4$ (0.02 mmol, 0.1 equiv), 1,3-bis(diphenylphosphoino)propane (0.024 mmol, 0.12 equiv), and DCE (0.4 mL) were added to a 1 dram reaction vial (polytetrafluoroethylene cap). The mixture was stirred at room temp for 1 h and then transferred to a 20 mL scintillation vial containing the mixture of starting material esters **16f** and **16m** or products **17f** and **17m** (0.1 mmol each, 0.2 mmol total, 1 equiv total) and toluene (1.6 mL). The reaction mixture was maintained at 150 °C for a specified time. The mixture was then removed from the glovebox and concentrated. The crude product was purified by flash column chromatography (gradient, EtOAc:Hex) to afford the oxyacylation product(s).

Partial Crossover Oxyacylation Reactions. In a nitrogen filled glovebox, $Rh(cod)_2BF_4$ (0.01 mmol, 0.1 equiv), 1,3-bis(diphenylphosphoino)propane (0.012 mmol, 0.12 equiv), and DCE (0.4 mL) were added to a 1 dram reaction vial (polytetrafluoroethylene cap). The mixture was stirred at room temp for 1 h and then transferred to a 1 dram vial containing starting material ester **16f** or product **17f** (0.1 mmol, 1 equiv) and phenol **10a** (0.1 mmol, 1 equiv) in toluene (1.6 mL). The reaction mixture was maintained at 150 °C for a specified amount of time. The mixture was then removed from the glovebox and concentrated. The crude product was purified by flash column chromatography (gradient, EtOAc:Hex) to afford the oxyacylation product(s).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b03011.

NMR spectra for new compounds, tabulated X-ray diffraction data, and NMR spectra for crossover experiments (PDF)

X-ray crystallographic data for **5** (CIF)

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Notes

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